ORIGINAL RESEARCH

Retrospective cohort study of the efficacy of caprylic triglyceride in patients with mild-to-moderate Alzheimer's disease

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Background: The purpose of this study was to evaluate the effects of caprylic triglyceride (CT) in patients with mild-to-moderate Alzheimer's disease (AD) in routine clinical practice via review of medical records and caregiver questionnaires.

Methods: Participants were outpatients aged ≥ 50 years with a diagnosis of probable mild-to-moderate AD who had received CT for ≥ 6 months. The primary outcome was change from baseline in the patient's condition as rated by the treating physician using a physician's overall assessment.

Results: A total of 55 patients were included. The physician's overall assessment indicated that ~80% of patients who had CT added to ongoing pharmacotherapy were stable or improved. Mini-Mental State Examination scores also remained stable over 15 months of therapy (20.6 ± 3.0 at baseline and 20.1 ± 5.6 at follow-up, $P = 0.5233$, n = 27). Caregiver assessments indicated that most patients were stable or improved with respect to memory and ability to carry out activities of daily living. The most frequent adverse events with CT involved the gastrointestinal system.

Conclusion: Results from this chart review indicate that addition of CT to pharmacotherapy was associated with stable disease or improvement over a follow-up period of 18.8 months.

Keywords: ketosis, cognition, Alzheimer's disease, metabolism, caprylic triglyceride

Introduction

Alzheimer's disease (AD) is the most common neurologic condition affecting the elderly in the US. The cost associated with AD is currently high and is expected to grow over the next 40 years. Total payments in 2012 for health care and long-term care services for people with AD and other dementias are expected to be $200 billion (not including the contributions of unpaid caregivers).[1] The cost of care for AD in the US is expected to rise above $1 trillion by 2050.[2]

Pharmacologic strategies for the treatment of AD have focused on modulating disease-associated neurotransmitter alterations.[3] Two classes of pharmacologic agents approved for treatment of AD are cholinesterase inhibitors and an N-methyl-D-aspartate receptor antagonist.[3–5] These agents are considered symptomatic treatments based on their ability to slow the clinical progression of symptoms across cognitive, behavioral, and functional domains. They do not provide detectable and sustained improvements in cognitive function above baseline.[3–5] New therapies are needed.

The brains of patients with AD display progressive, region-specific declines in the cerebral metabolic rate of glucose,[6] and these changes are apparent early in the course of AD before there is demonstrable cell loss and plaque deposition.[7]

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Under most conditions, cerebral metabolism is fueled almost exclusively by glucose. However, under certain conditions, such as neonatal development and extended fasting, the brain will derive much of its energy from ketone bodies.[8,9] Ketone bodies are comprised of beta-hydroxybutyrate, acetoacetate, and acetone. They are normally derived from fat stores and offer an alternative fuel for brain metabolism. Therefore, if cerebral glucose metabolism is compromised in the AD patient, perhaps ketone bodies can substitute for glucose and improve cognitive performance.[9,10] Ketone bodies are an efficient fuel for cells,[11,12] and results from preclinical studies have suggested that induced ketosis may be beneficial in AD.[13,14] In addition, studies have suggested that ketone bodies may be useful in a variety of neurologic disorders.[15]

A previous study has demonstrated that administration of 20 g of caprylic triglyceride (CT) increases blood levels of beta-hydroxybutyrate (the major ketone body in humans) 2 hours post dose to a mean value of 0.39 mM, and this therapy has been shown to be beneficial in patients with mild-to-moderate AD.[10,16] CT is composed of a glycerol backbone and three caprylic (C8:0) fatty acid chains, well known for their ketogenic properties.[17] The efficacy and safety of a medical food containing CT in subjects with mild-to-moderate AD has been demonstrated in a multicenter, randomized, double-blind, placebo-controlled study that included 152 outpatients with probable mild-to-moderate AD.[10]

It is important to continue evaluations of interventions in routine clinical practice. This approach has been taken with pharmacotherapies for AD,[18–20] and CT should be evaluated in a similar manner. The primary objective of this study was to assess patient outcomes of CT used alone or in combination with ongoing pharmacotherapy in mild-to-moderate AD in routine clinical practice. Due to the small number of patients enrolled in the study, the results should be considered exploratory.

Materials and methods
Study design
Patient outcomes were evaluated by chart review carried out at 11 practices in which CT was prescribed in patients with mild-to-moderate AD. Investigators at each site were instructed to review all charts for patients who were taking or had taken CT and determine their eligibility for the study. The criteria for inclusion were male or female outpatients aged ≥50 years with a diagnosis of probable AD of mild-to-moderate severity; Mini-Mental State Examination

(MMSE) score between 14 and 24 inclusive at the initiation of CT (if available), or diagnosis of mild-to-moderate AD; and receipt of CT for ≥6 months. Potential patients were excluded if they had an MMSE score <14 at the time when CT was initiated or comorbid disease known to adversely impact cognitive function (eg, Parkinson's disease, history of cerebral infarcts, dementia with Lewy bodies, vascular dementia). Approximately 200 patients were to be enrolled in the study. The sample size was based on estimates of numbers of patients who were available for inclusion as reported by participating physicians, and not based on any statistical considerations. After an independent evaluation of potential patients, only 55 were found to be eligible for participation. The trial was carried out with institutional review board approval. Patients and caregivers were required to provide written informed consent prior to inclusion of their information in the study. This study is registered at http://www. clinicaltrials.gov/ct2/show/NCT01538212.

A caregiver was defined to be at least 21 years of age (this age was believed to be appropriate for a caregiver who would provide a patient assessment as part of the study), had been the primary caregiver since prior to the initiation of CT, provided at least 4 hours of supervision or direct assistance per day for the patient, and was able to perform assessments.

Assessments
Two primary measures were used to assess the patient's response to CT. The first was the physician's overall assessment of patient status at the most recent evaluation on CT. The second was the change in MMSE score from initiation of CT to the most recent MMSE assessment on CT. The physician's overall assessment of patient status comprised three simple evaluations. First, status at initiation of CT therapy, scored as check boxes of: mild AD or moderate AD. Second, status at most recent evaluation, scored as check boxes of: mild AD, moderate AD, severe AD, very severe AD. Third, change from beginning of CT to present, scored as check boxes of: marked improvement, moderate improvement, improvement, stable, worsening, moderate worsening, or marked worsening.

Secondary measures included changes from baseline in patient's living situation; medication changes for the management of AD and for psychiatric symptoms related to AD; changes in patient's memory and ability to carry out instrumental activities of daily living as assessed by caregivers; and adverse events. Caregiver questionnaires

were also employed to determine CT dosing frequency (number of days per week); to estimate routine dose level (full dose or less than a full dose is generally taken); and adherence to CT (if available). Caregivers were also asked to assess the patient's memory since initiation of CT, based on a modified version of the Memory Complaints Questionnaire developed by Memory Assessment Clinics; and ability to carry out activities of daily living adapted from Lawton and Brody.[21]

Data analysis

Scores from the physician's overall assessment of change from baseline after initiation of CT were summarized with descriptive statistics. The primary analysis of the MMSE was a paired *t*-test of baseline score and last available score while on CT. Changes from baseline in caregiver assessments of patients' ability to use the telephone, prepare food, and dress were evaluated with Mann–Whitney *U*-tests. All statistical tests were two-sided and were carried out at the 5% level of significance. Results for all demographic and secondary study endpoints were tabulated and appropriate descriptive statistics were calculated. Pearson correlation between physician's overall assessment of change and caregiver assessment was performed with R 2.15.0 (www.r-project.org).

Results
Records reviewed

A total of 437 records were reviewed at 11 study sites, and those of 55 patients who met the inclusion and exclusion criteria and provided informed written consent were included in the analysis. The most common reasons for exclusion were MMSE scores out of the designated inclusion range, taking CT for <6 months, no formal diagnosis of AD, and comorbidities that may have affected cognitive function. Caregiver questionnaires were filled out for a total of 26 patients. A minimum of 28 hours of caregiving per week was set as a criterion for inclusion in the study protocol. Five caregivers did not meet this minimum, and were not included in the analysis.

The demographic and clinical characteristics of the patients whose records were analyzed are summarized in Table 1. Nearly all patients (96.4%) were receiving medications indicated for the treatment of AD; and 54.6% were receiving agents indicated for other psychiatric symptoms (most often depression). At baseline, 88.7% of patients were living with caregivers (relatives) and 11.3% were residing in assisted living facilities.

Table 1 Demographic and clinical characteristics of patients whose records were reviewed

Characteristic	N = 55
Sex, n (%)	
Male	31 (56.4)
Female	24 (43.6)
Age, years (mean ± SD)	79.7 ± 7.46
Duration of disease since formal diagnosis, years (mean ± SD)	3.0 ± 1.96
Basis of AD diagnosis, n (%)	
Signs and symptoms	55 (100)
Computed tomography	14 (25.4)
Magnetic resonance imaging	21 (38.2)
Cognitive testing	50 (90.9)
Electroencephalography	9 (16.4)
Disease severity at baseline, n (%)	
Mild	24 (43.6)
Moderate	31 (56.4)
AD treatment at baseline, n (%)*	
Memantine	48 (87.3)
Donepezil	24 (43.6)
Rivastigmine patch	18 (32.7)
Galantamine	3 (5.4)
None	2 (3.6)
Mean duration of CT in months ± SD (range)	18.8 ± 9.2 (6–39)
Living arrangement, n (%)	
With caregiver	47 (88.7)
Assisted living facility	6 (11.3)
Concomitant medications for neuropsychiatric conditions, n (%)**	
Escitalopram	8 (14.5)
Citalopram	7 (12.7)
Duloxetine	5 (9.1)
Alprazolam	5 (9.1)
Bupropion	4 (7.3)
Quetiapine	4 (7.3)
Dextromethorphan	3 (5.4)
Venlafaxine	3 (5.4)
Mirtazapine	2 (3.6)
Sertraline	2 (3.6)
Aripiprazole	1 (1.8)
Valproate	1 (1.8)
Modafinil	1 (1.8)
Amphetamine	1 (1.8)
Lamotrigine	1 (1.8)
Desvenlafaxine	1 (1.8)
Ziprasidone	1 (1.8)
None	25 (45.5)

Notes: *Multiple evaluations were possible; **patients may have been taking more than one medication.
Abbreviations: AD, Alzheimer's disease; CT, caprylic triglyceride; SD, standard deviation.

CT dosing

Patients who had received CT, regardless of the dose, for 6 months or longer were eligible for the study. For the 55 patients whose records were reviewed, the mean duration

of CT was 18.8 ± 9.2 months. Chart review indicated that most patients (89.1%) were titrated to a full 20 g daily CT dose. The remainder (10.9%) received 10 g per day.

Patient outcomes
Primary measures
Physician's overall assessment of changes from baseline in patient status (Figure 1A) were marked improvement for 5.5%, moderate improvement for 5.5%, improvement for 24.1%, stable for 44.4%, worsening for 14.8%, moderate worsening for 3.7%, and marked worsening for 1.8%. MMSE scores at baseline and while on CT were available for 27 patients. The mean baseline score for these patients was 20.6 ± 3.0 and that for the most recent measurement on CT was 20.1 ± 5.6 (difference −0.48, 95% confidence interval −1.05 to 2.01, $t = 0.6470$, $P = 0.5233$).

Secondary measures
At baseline, 43.6% of patients were rated by their physicians as having mild AD and 56.4% were considered to have moderate AD. Of the 55 participants, 80% (n = 44) did not change in severity of disease, while 20% (n = 11) were diagnosed with a more advanced disease state (Figure 1B).

No patients whose records were reviewed had changes in their living situation during CT therapy. There were also few changes in medications patients were taking for AD; 87.3% of patients had no changes; 7.3% had switches or augmentation in pharmacotherapy, and 5.4% had addition of a medical food that included phosphatidylserine enriched with docosahexaenoic acid. Pharmacotherapy for psychiatric/behavioral symptoms also remained stable for most patients (70.9%). There were 25 patients taking no medications for psychiatric illness at baseline and six of these (10.9% of all patients, 24.0% of those not

taking psychiatric medications at baseline) had agents added to therapy, most often antidepressants or atypical antipsychotics. In addition, 33.0% of patients receiving medications at baseline had switches and/or additions to their therapy. These changes most often included switching and/or augmentation of antidepressant treatment and addition of an anxiolytic.

Results from caregiver surveys
Caregivers' responses indicated that addition of CT to therapy resulted in some degree of improvement or stability in remembering the name of a person to whom they were just introduced in 80.9% (17/21) of patients, recalling telephone numbers or zip codes that were used on a daily or weekly basis in 80.9% (17/21), and in finding commonly used objects in 85.7% (18/21), as shown in Figure 2. Overall assessments of memory also indicated that the majority of patients (75.0%) (15/20) were stable or improved over the follow-up period (Figure 2). Assessment of ability to use the telephone, prepare food, and dressing indicated no significant changes from baseline (Mann–Whitney U-tests, $P = 0.696$, $P = 0.904$, and $P = 0.596$, respectively).

Correlation between physician and caregiver assessments
Caregivers and physicians may assess a change in patient status differently. However, a significant correlation was found between the physician's overall assessment of change and caregiver surveys ($r = −0.5423$, confidence interval −0.80 to −0.12, $P = 0.016$, Figure 3).

Safety outcomes
Of the 55 patients whose charts were reviewed, 41 (74.5%) had no adverse events. The remaining 14 patients had a
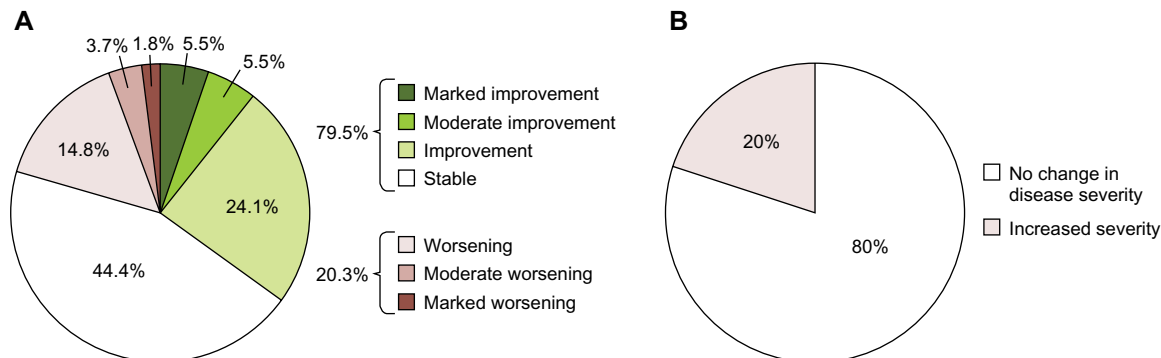
Figure 1 Physician's overall assessment of change from baseline. (**A**) Pie chart depicting overall change in patients. Green shading indicates improvement, red shading indicates worsening, and white represents stable status. (**B**) Percent of patients with change in severity of disease compared with initiation of caprylic triglyceride (CT). Mean duration of therapy 18.8 months.
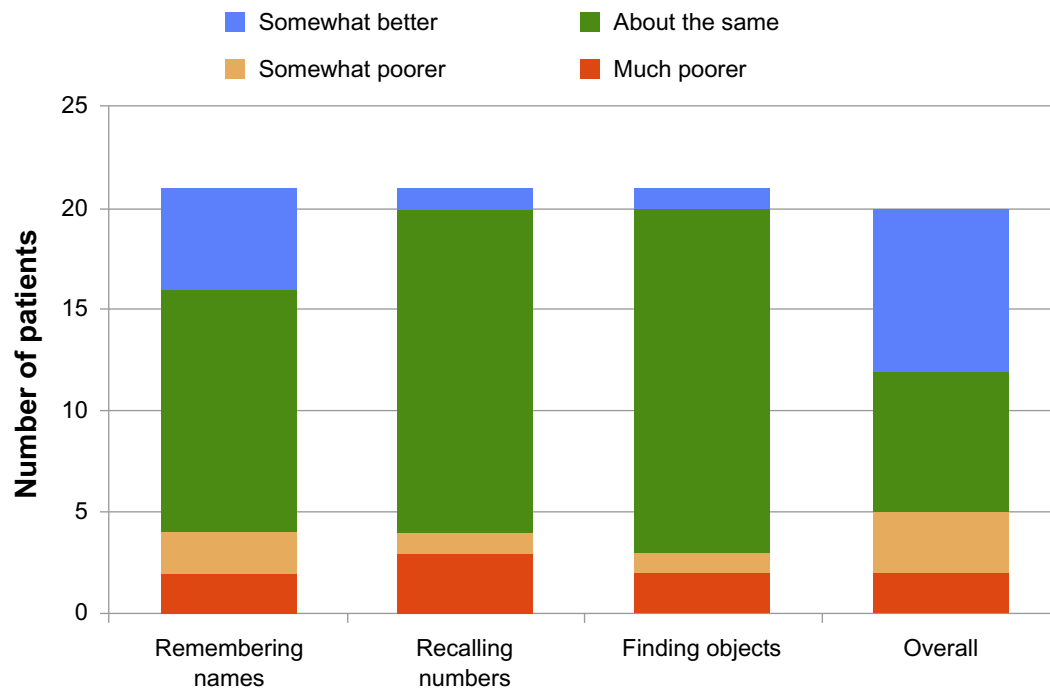
Figure 2 Caregiver assessment of memory function.
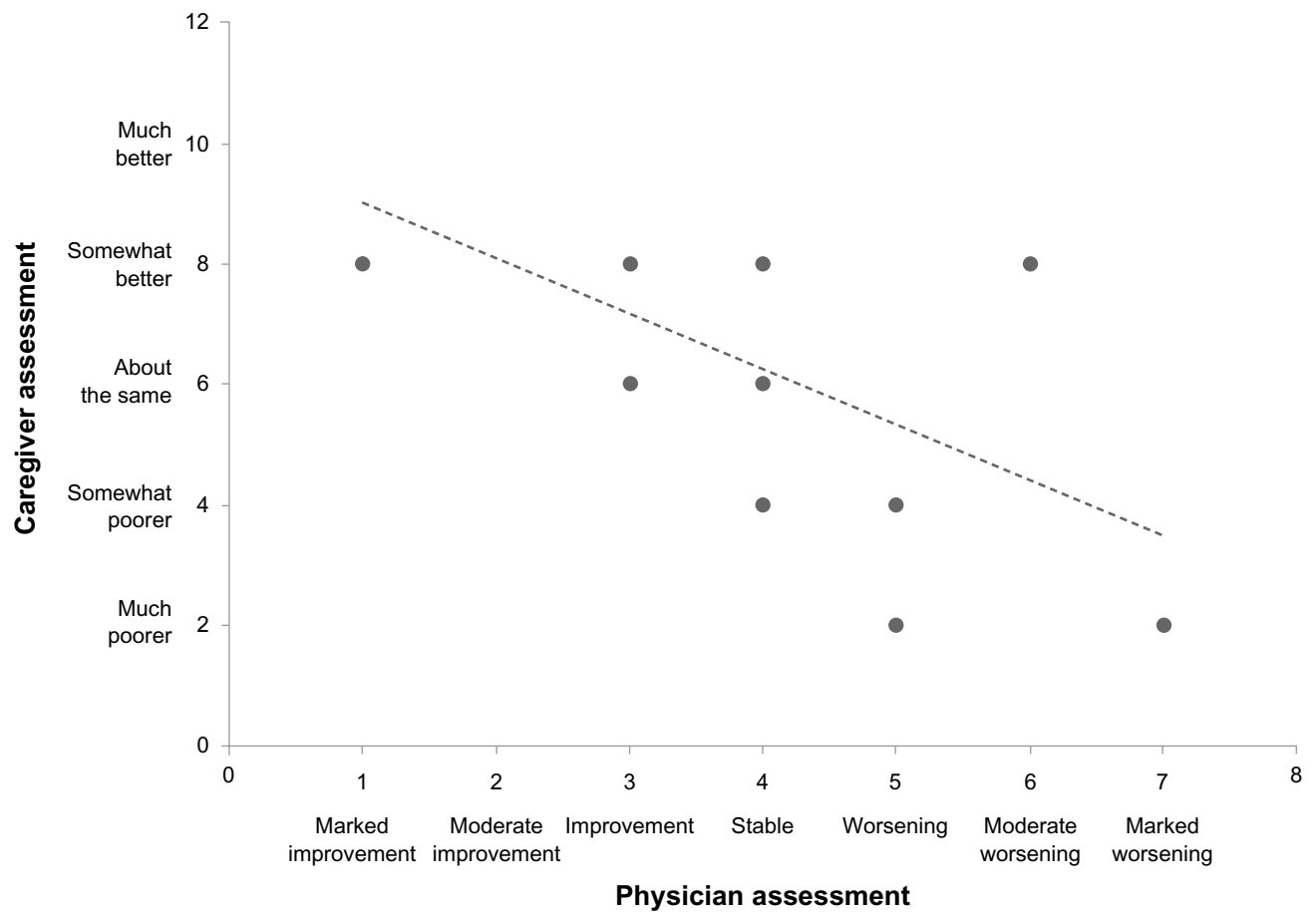

Figure 3 Correlation of results between physician and caregiver assessments.

total of 30 adverse events, eight of which were considered to be related to CT. All related adverse events involved the gastrointestinal system. There was one severe adverse event, a brain tumor that was not related to CT. A total of eight patients (14.5%) discontinued CT and four of these (7.3%) discontinued due to adverse events. All adverse events are summarized in Table 2.

Discussion

Results from this chart review suggest that CT helped to stabilize or improve the clinical status and cognitive function in patients receiving therapy for a mean of approximately 19 months. The physician's overall assessment of change from baseline indicated that 79.5% of patients either showed improvement or remained stable, while 20.3% worsened. Results for the 27 patients for whom MMSE scores were available at baseline and on therapy indicate that, on average, patients remained stable with no significant change over a mean of 15 months of follow-up. No patients had changes in their living situation during CT therapy, and most patients remained stable with respect to medications for AD and those for psychiatric/behavioral conditions. The adverse event most often associated with CT was mild gastrointestinal upset. Caregiver assessments also indicated stability or improvement in cognitive function and no significant changes in

Table 2 Adverse events

Adverse event	N = 55 %
Gastrointestinal upset	14.5
Diarrhea	1.8
Lightheadedness	1.8
Dizziness	1.8
Irritable bowel syndrome	1.8
Disturbed balance	1.8
Disturbed vision	1.8
Impaired consciousness	1.8
Slurred speech	1.8
Fatigue	1.8
Leg cramp	1.8
Confusion	1.8
Urinary frequency	1.8
Brain tumor	1.8
Agitation	1.8
Pernicious anemia	1.8
Ankle pain	1.8
Weight loss	1.8
Upper respiratory infection	1.8
Fall with hip fracture	1.8
Hypervitaminosis (B12)	1.8
Hospitalization (failure to eat)	1.8
Headache	1.8

the ability to carry out activities of daily living. There was a significant correlation between physician and caregiver assessment of patient outcomes.

The physician's overall assessment indicated that ~80% of patients who had CT added to their ongoing pharmacotherapy were stable or improved. A large number of different global severity/status scales have been employed in assessing effects of treatment in patients with AD. That most similar to the measure employed in this study is the Clinical Global Impressions of Change, which provides minimal instructions to the rater.[22] Results from global assessments of the type carried out in this study have also been shown to be well correlated with quantitative measures of cognitive function/dementia.[23]

The MMSE is the most widely used brief mental status screening instrument,[24,25] and has been used extensively for evaluation of patients with AD in both clinical trials and follow-up of patients being managed in routine clinical practice.[26–29] In order to evaluate the impact of CT on mild-to-moderate AD in routine practice, comparison with subjects on standard therapy without CT was examined by literature review. This approach permitted comparison of the present results with those from much larger numbers of patients receiving pharmacotherapy for AD. A summary of results from clinical trials and epidemiologic studies published prior to 2005 indicated a decline in MMSE scores of 0.6–4.4 points per year in different studies.[30] More recently, a study of 686 patients with mild-to-moderate AD with 90% receiving AD-specific medication indicated an annual decline in MMSE scores of 2.4 points per year.[31] In comparison, the decline in MMSE scores over 15 months in the present study was 0.48 and not statistically significant. It should be noted that there are limitations to the use of the MMSE for assessment of cognitive function, particularly when comparisons are made across studies. The rate of change for MMSE has been shown to be strongly influenced by the baseline score.[32,33] Other variables, including patient age, duration of AD, and education, have been linked to rate of decline for MMSE scores, but these relationships appear to be weaker and more variable than those for baseline MMSE score.[34–40] Thus, comparison of results from the present chart review and those from other studies should be undertaken with caution.

Caregiver assessments also indicate that memory and ability to carry out activities of daily living remained stable or improved during therapy with CT. In an assessment of overall memory, 40% of the caregivers reported somewhat better or much better memory after initiation of CT.

Functional impairments in AD place the greatest burden on both caregivers and the economy;[41] and results from several studies have suggested that neuropsychologic test performance is predictive of activities of daily living performance in patients with AD.[42,43] Results from observational studies and clinical trials indicate that deterioration in the ability to carry out activities of daily living can be detected among patients with AD over follow-up periods comparable with that in the present study.[44,45]

Changes in the requirement for psychiatric medications were used as a surrogate measure for effects of CT on neuropsychiatric symptoms. These symptoms are a source of caregiver burden and are associated with increased probability of institutionalization.[46] Treatment aimed at improving cognition in patients with AD has also been shown to decrease the severity of neuropsychiatric symptoms.[47] Results from the record review indicate that medications for psychiatric illness remained stable for most patients during the period of CT.

Results from the chart review indicated the adverse event most often associated with CT was gastrointestinal upset and that this event led to discontinuation in 7.3% of patients. Most patients (89.1%) were titrated to a full 20 g daily CT dose and maintained at this dose. While the presumed mechanism of action of CT is the induction of ketosis and subsequent provision of ketone bodies as an alternative fuel for neurons, ketone bodies have been shown to have other neuroprotective effects that may be beneficial, not only in AD but also in other neurologic conditions.[15] However, it is important to note that there have been reports of detrimental effects of caloric restriction and ketogenic diets on neurologic function.[48,49] However, induction of mild ketosis by CT does not require restriction of macronutrients, and therefore may not lead to the detrimental effects attributed to ketogenic diets.

One limitation of this study was that the Apolipoprotein E4 (*APOE4*) carriage status was evaluated and recorded in the medical records of only seven patients (two were *APOE4*-positive). Prior clinical results for CT indicated significant efficacy in *APOE4*-negative but not *APOE4*-positive patients.[10,16]

In conclusion, results from this small chart review study indicate that addition of CT to pharmacotherapy for AD was associated with stable disease or improvement for most patients over a follow-up period of 18.8 months. Addition of CT was also associated with stabilization or improvements in the ability to carry out activities of daily living for most patients and warrants further investigation in a larger study.

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